NOVARTIS

Clinical Development

TIN816

CTIN816B12201 / NCT05507437

# A multicenter, participant and investigator-blinded, randomized, placebo-controlled Phase 2a study to investigate the pharmacokinetics, safety and tolerability of TIN816 in the treatment of patients with sepsis-associated acute kidney injury

## Statistical Analysis Plan (SAP)
## Amendment 2

| | |
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## Document History – Changes compared to previous final version of SAP

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| *04-Apr-2023* | | Adding screening set<br>Adding immunogenicity set<br>Adding mean arterial pressure figure and its definition<br>[redacted] | *The outputs were not generated yet* | |
| *10-May-2023* | | Adding raw and normalized PK results due to dosing error | | *Section 2.5* |
| [redacted] | | [redacted] | | [redacted] |
| *20-May-2024* | | Updating treatment emergent adverse event summary<br>[redacted] | | *Section 2.6*<br>[redacted] |

## Table of contents

## List of tables



## List of figures

## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AKI | Acute Kidney Injury |
| AUC | Area Under Curve |
| BMI | Body Mass Index |
| CSR | Clinical Study Report |
| CV | Coefficient of Variation |
| eGFR | Estimated Glomerular Filtration Rate |
| EOS | End of Study |
| FAS | Full Analysis Set |
| FIH | First In Human |
| GCV | Geometric Coefficient of Variation |
| HV | Health Volunteers |
| IA | Interim Analyses |
| ICF | Informed Consent Form |
| IV | Intravenous |
| KDIGO | Kidney Disease Improving Global Outcomes |
| LLOQ | Lower Limit of Quantification |
| LOCF | Last Observation Carried Forward |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PT | Preferred Term |
| RRT | Renal Replacement Therapy |
| SA-AKI | Sepsis-Associated Acute Kidney Injury |
| SAF | Safety set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SCR | Screening set |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |
| SOFA | Sequential Organ Failure Assessment |
| ULOQ | Upper Limit of Quantification |

# 1 Introduction

The purpose of the document is to describe the statistical analyses to be included in the clinical study report (CSR) to be produced at the time the last patient has completed the study CTIN816B12201. The document covers the safety analysis and the efficacy analysis on the data in the study.

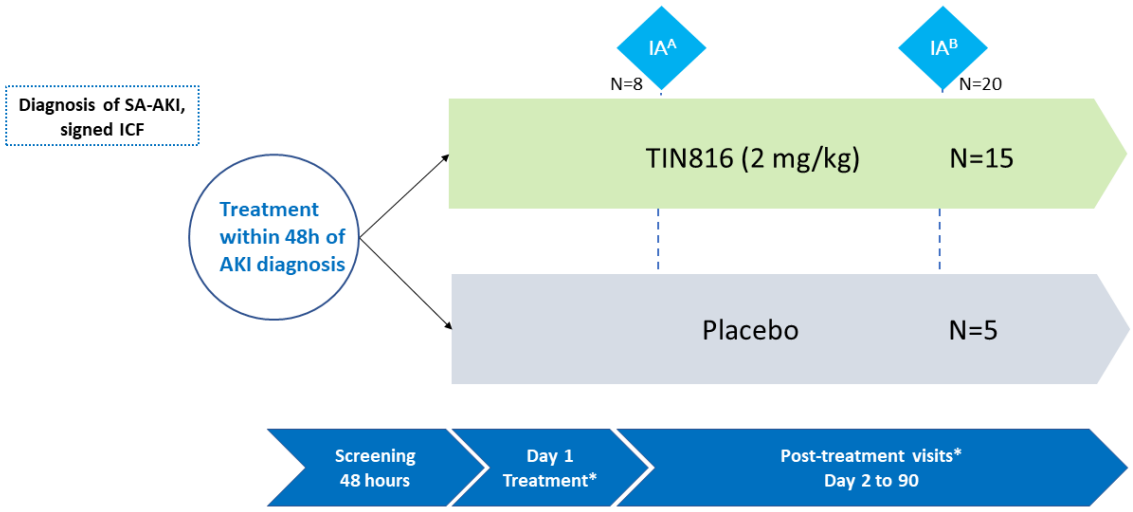
## 1.1 Study design

This is a multicenter, participant and investigator-blinded, randomized, placebo-controlled study to characterize PK/PD profile and to evaluate the safety and the efficacy of TIN816 in hospitalized adult participants with diagnosis of sepsis and acute kidney injury (AKI). Approximately 20 participants will be randomized in the study. The study consists of a screening period (up to 48 hours), treatment period (Day 1), and post-treatment period (Day 2 to 90) and is summarized in Figure 1-1.

An interim analysis (IA) is planned when approximately 8 participants complete Day 14 visit. The study will continue without modification if a similar PK profile of TIN816 compared to the one in the healthy volunteers (HV) is confirmed. Otherwise, an adaptive design would be implemented with options to add up to two additional arms testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion.

The adaptive design will be supported by modeling and simulation with data from the preclinical studies, first in human (FIH) study and the IA of the current PK/PD study. Patient recruitment will continue during the IA to enroll up to a cap of 12 patients. In the circumstance that the first IA does not provide sufficient PK data to support phase 2b, an additional IA will be added when all 20 patients complete Day 14 visit.

**Figure 1-1 Study design**




[A] interim analysis (IA) based on 8 patients with 14-day data collected from baseline
[B] conditional additional interim analysis (IA) based on 20 patients with 14-day data collected from baseline
* participant-investigator blinded

## 1.2 Study objectives and endpoints

**Table 1-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To assess pharmacokinetics (PK) of TIN816 with a single dose of IV infusion | • TIN816 concentrations in serum<br>PK parameters: $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$ of TIN816 |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To assess safety and tolerability of TIN816 vs placebo | • Safety evaluations (including adverse events/serious adverse events, safety laboratory parameters, vital signs and immunogenicity) |

### 1.2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during study conduct which could impact the interpretation of the study results (eg. premature discontinuation of treatment).

The primary clinical question of interest is: What are the pharmacokinetic characteristics (systemic exposure) of TIN816 (IV infusion) in hospitalized adult participants with diagnosis of SA-AKI, who received the complete treatment infusion?

The primary estimand is described by the following attributes:

1. Population: hospitalized adult patients with diagnosis of SA-AKI with complete IV infusion and at least one available valid PK concentration measurement who survived at Day 7.
2. Primary endpoint: PK parameters, including $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$.
3. Treatment of interest: A single dose of investigational study treatment TIN816 will be administered via an IV infusion.

4. Handling the intercurrent events: PK will be evaluated in patients who remain alive until Day 7.
5. The summary measure: geometric mean and median.

### 1.2.2 Secondary estimands

As the intention of estimand framework is applied to efficacy endpoints, considering all safety outcomes are the secondary endpoint, the estimand framework for secondary estimands is not further discussed.

### Estimand considerations in case of COVID-19 pandemic impact

The overarching principle for primary and secondary estimands is answering questions of interest regarding the treatment effect of TIN816 that are valid in conditions when the COVID-19 pandemic is no longer present.

It is not known whether TIN816 (recombinant CD39) can influence the clinical course of an infection with coronavirus SARS-CoV-2 (COVID-19). TIN816 is designed to treat acute organ injuries. Data capture and clinical evaluation activities include possible adaptations to restrictions for participant access to investigational sites in case of a new infection wave. Additional supplementary analysis as well as sensitivity analyses may be performed due to the presence of a considerable amount of deviations from the normal methods of participant follow up and data capture or other pandemic-related intercurrent events.

# 2 Statistical methods

## 2.1 Data analysis general information

Data will be analyzed according to Section 9 of the CTIN816B12201 Clinical Trial Protocol. The most recent version of the SAS® and R software available in the statistical programming environment will be used for the analysis.

In general, categorical data will be presented as frequencies and percentages in descriptive statistics. For continuous data, mean, standard deviation, median, minimum and maximum will be presented. For selected parameters, 25$^{th}$ and 75$^{th}$ percentiles will also be presented.

For PK parameters, n, mean, median, minimum, maximum, coefficient of variation (CV (%)) to mean, geometric mean, and CV (%) to geometric mean will be presented.

### 2.1.1 General definitions

The term "**study treatment**" and/or "**study drug**" refers to the 2-hour study infusion drug during the study, that is TIN816 2 mg/kg.

For analysis purposes, "**Baseline**" is defined to be the last result obtained at or prior to start of study treatment (Day 1) for baseline demographics, medical history, lab values, vital signs and ECGs. Most variables will have their baseline at Day 1, unless otherwise specified. For assessments not performed at Day 1, the assessment at the screening visit or most recent assessment prior to start of study treatment will be used as baseline.

[redacted]

The reference creatinine baseline is defined as below.

For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI should be used as reference baseline, otherwise, baseline serum creatinine in the following order of preference:

1. Median value within 3 months of the hospital admission. If not available:
2. Median value between 3 and 6 months prior to hospital admission. If not available:
3. At hospital admission.

**"Post-Baseline"** is defined for analysis purposes to be any value collected after the "baseline" as defined above for analysis purposes.

The term **"study day"** is defined relative to the analysis reference date, which is the date of first administration of study treatment.

The *study day* for a scheduled or unscheduled visit on or after the analysis reference date is defined as:

*Study day* = (Date of Visit) – (analysis reference date) +1.

The *study day* for a scheduled or unscheduled visit before the analysis reference date is defined as:

*Study day* = (Date of visit) – (analysis reference date).

Thus the analysis reference date (date of first administration of study treatment) will be study day 1 and the date directly prior the analysis reference date will be study day □1 (there is no study day 0).

The term **"unscheduled visit"** refers to visits that occurred not as part of the Clinical Trial Protocol assessment schedule. Data collected at unscheduled visits will, in general, not be used in 'by-visit tabulations' or graphs, but they will be included in analyses of safety parameters based on all post-baseline values such as summary statistics of clinically notable abnormalities of laboratory data. For efficacy evaluations, measurements from unscheduled visits will generally not be used, unless where otherwise specified. All data collected at both scheduled and unscheduled visits will be included in data listings.

"**Completion**": a participant will be considered to have completed the study when the patient has completed the Day 90 visit in the study or End of Study (EOS) for participants who discontinue from the study. The maximum of the date of last visit in the randomized treatment period, date of withdrawal of consent (in case of withdrawal from study), would be the date of **last contact** for the patient in the study.

## 2.2 Analysis sets

The Screening set (SCR) consists of all patients who have been screened. The purpose of the screening set is to describe the number of patients in screen failures. Screen failures are the patients included in the screening set but not randomized.

The Randomized Analysis Set (RAS) consists of all randomized participants. This analysis set will not be used for any analyses and is solely intended for providing complete information on how participants were randomized.

The PK analysis set will include all participants who receive treatment and survive Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration. The PD analysis set will include all participants who receive treatment with available PD data. Participants will be analyzed according to actual study treatment received.

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. Mis-randomized participants, that is, participants who were randomized incorrectly and did not receive any study drug will be excluded from this set. This will be the analysis set used for all efficacy analyses.

The safety set (SAF) includes all participants who received one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the participant took at least one dose of that study treatment regardless treatment group randomized to. This will be the analysis set used for safety analysis except for PK/PD analysis.

Immunogenicity set includes all subjects in the Safety set with a non-missing baseline anti-drug antibodies (ADA) result or at least one non-missing post-baseline ADA result.

## 2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the FAS by treatment group. In addition, summaries of relevant past or current medical conditions will be presented.

Categorical data will be presented as frequencies and percentages. The summary statistics shown for continuous data will be n, mean, standard deviation, median, minimum, and maximum.

### 2.3.1 Patient disposition

The number of patients screened, screened but not enrolled, completed and discontinued from the study will be summarized. The reasons for screen failure will be provided for the FAS by treatment group. Patients discontinued from the study will also be summarized with reasons for discontinuation. If the disposition is related to COVID-19, the relationship to COVID-19 will also be presented.

The number of subjects with protocol deviations will be tabulated by deviation category as well as deviation related to COVID-19 for the FAS. The number of patients by country will also be presented.

Demographic and baseline characteristics table include but not limited to the following information:

- Informed consent provider (Self/Legal guardian)
- Age
- Sex
- Ethnicity
- Race
- Weight [kg]
- Height [cm]
- Body mass index (BMI) [$kg/m^2$]
- Smoking history
- Alcohol history
- Baseline serum creatinine value (as defined above in Section 2.1.1)

Sepsis diagnosis characteristics at screening visit and APACHE II score at Day 1 include the following information:

- SOFA score $\geq 2$ (yes/no)
- Septic shock (yes/no)
- Presumptive source of the infection
- Blood culture performed (yes/no)
  - Positive: Gram positive bacteria, Gram negative bacteria, fungal infection, other
  - Negative
- APACHE II score

AKI diagnosis at screening visit include but not limited to following information:

- Diagnosis of AKI based on KDIGO Serum Creatinine criteria (yes/no)
- Stage of AKI stage based on DKIGO criteria
- Serum creatinine level
- Urine output
- Fluid resuscitation (yes/no)
- Vasopressor (yes/no)
- Renal replacement therary (yes/no)
- Mechanical ventilation (yes/no)

### 2.3.2 Relevant Medical History and current medical conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology using the most recent version at the time when the last patient has

completed the study. Medical history terms will be summarized by primary system organ class and preferred term.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Study treatment / Treatment of interest

The "treatment of interest" is a single dose of investigational study treatment TIN816 administered via an IV infusion.

The Safety set (SAF) will be used for the analyses below, unless otherwise specified. Descriptive statistics will be provided.

#### Duration of study period

The "duration of study" will be computed as the time from the date of first study treatment administration to the minimum of the following:

- Date of the last visit
- Date of participant's death
- Date of participant's withdrawal of consent

#### Dose Exposure

The duration of exposure (in hours) to study treatment will be computed and summarized, but excluding temporary treatment interruptions.

Total volume (ml) administered will also be summarized.

### 2.4.2 Prior, concomitant and post therapies

Analyses in this section will be based on the SAF. Descriptive statistics will be provided.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken at least a day prior to the start of study treatment (Day 1).

Concomitant medications and significant non-drug therapies are defined as those taken at or after the start of study treatment (i.e. with end date on or after Day 1, ongoing at EOS or with missing end date and start date prior to the end of study treatment).

Medications and significant non-drug therapies that started prior and were also continued after the start of study treatment (Day 1) will be considered both as Prior and Concomitant.

Prior or concomitant medications and significant non-drug therapies will be listed and summarized in separate tabulations based on the latest version of the coding dictionary. Medications will be presented in alphabetic order, according to the Anatomical Therapeutic Chemical (ATC) classification system and by preferred term (PT). Tables will show the number and percentage of participants receiving at least one drug of a particular PT and at least one drug in a particular ATC class.

## 2.5 Analysis supporting primary objective

The primary endpoint analysis will be based on PK population.

### 2.5.1 Primary endpoint(s)/Primary estimand(s)

The primary endpoint is all TIN816 concentrations in serum PK parameters, including $C_{max}$ , $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$, and other relevant PK parameters (data permitting) (Table 2-1). It will be summarized descriptively for participants with at least one dose of study treatment.

There is no inferential analysis to be performed.

TIN816 serum concentration data will be listed by treatment, participant and visit/sampling time point. Descriptive summary statistics of TIN816 serum concentration data will be provided by treatment, and visit/sampling time point, including the frequency of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. PK data will also be represented graphically (including spaghetti plots, and mean plots with SD) by treatment arm, participant and visit. Overlaying individual serum concentration-time profiles will be generated by treatment arm participant and visit/sampling time point.

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters. Pharmacokinetic parameters will be calculated as described in CTIN816B12201 Protocol and will be listed by treatment and participant and summarized by treatment with descriptive statistics as listed below.

The pharmacokinetic parameters listed in the table below will be determined from the serum concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher). Other relevant PK parameters may be added (data permitting).

**Table 2-1 Pharmacokinetic parameters from Non-compartmental analysis**

| PK parameter | Definition |
|---|---|
| $AUC_{last}$ | The area under the curve (AUC) from time zero to the last measurable concentration sampling time (Tlast) (mass × time × volume−1) |
| $AUC_{inf}$ | The AUC from time zero extrapolated to infinity (mass × time × volume−1) |
| $AUC_{inf}$ /D | The AUC from time zero to infinity (mass × time × volume-1), normalized by actual dose (mg/kg) |
| $AUC_{0\text{-}14d}$ | The AUC from time zero to 14 days post-dose (mass × time × volume−1) |
| $C_{max}$ | The maximum (peak) observed serum drug concentration after single dose administration (mass × volume−1) |
| $C_{max}$ /D | The maximum (peak) observed serum drug concentration after single dose administration (mass × volume-1), normalized by actual dose (mg/kg) |
| $T_{max}$ | The time to reach maximum (peak) serum drug concentration after single dose administration (time) |
| $T_{1/2}$ | The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time) |
| CL | The total body clearance of drug from the serum (volume × time−1) |
| $V_z$ | The apparent volume of distribution during terminal phase (associated with λz) (volume) |
| $V_{ss}$ | Estimate of the volume of distribution at steady state based on the last observed concentration (volume) |

Urine PK concentration will be provided as appropriate and a renal clearance (CLr) may be determined if data permit. In case a renal clearance is calculated, that parameter should be included in the tabulated statistical PK parameter output mentioned above. At least urine PK concentrations will be summarized as descriptive summary statistics, as done with serum PK concentrations.

### 2.5.2 Statistical hypothesis, model, and method of analysis

The analysis will be mainly based on summary statistics and no inferential statistical analysis is planned. The graphical summaries on PK concentration will also be provided.

### 2.5.3 Handling of intercurrent events

All PK data will be presented as recorded in the descriptive statistics. For participants who discontinue from study or death where PK information is not available, the impact of this on the interpretation of the results will be considered. Additional summaries as needed to support this interpretation may be presented. It is not intended to impute missing data after discontinuation.

### 2.5.4 Handling of missing values not related to intercurrent event

Missing primary endpoint values due to protocol deviations or other issues related to a pandemic are not anticipated as measures have been put in place, where possible, to allow for the protocol assessments to be conducted. In case missing values do occur for such reasons, only data available will be used.

### 2.5.5 Sensitivity analyses for primary endpoint/estimand

No sensitivity analyses are planned.

### 2.5.6 Supplementary analyses

In case PK profiles in patients are very different from those in healthy volunteers (HV), the PK profiles may be assessed using a population PK model to confirm dosing regimens that provide comparable exposure in patients as observed in HV. This analysis would be reported separately and is planned in a separate analysis plan.

[redacted]

### 2.5.7 Supportive analyses

No subgroup or supportive analyses are planned.

## 2.6 Analysis supporting secondary endpoints/estimands

The analysis for secondary endpoints will be based on descriptive statistics by treatment group.

### 2.6.1 Secondary endpoints/secondary estimands

For all safety analyses, the safety set will be used. All summaries where appropriate (e.g. change from baseline summaries), listings and tables will be presented by treatment group.

### Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of participant and investigator-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of participants with following adverse events of special interest/related to potential risks will be summarized by treatment:

- bleeding
- perivascular/vascular mineralization
- infusion reaction and hypersensitivity
- anti-drug antibody mediated reactions (immunogenicity).

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

The following adverse events will be counted during 90-day study period:

- These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

### Vital signs

Summary statistics will be provided for all vital signs data by treatment and visit/time. Where ranges are available, abnormalities (and relevant orthostatic changes) will be listed by treatment group, participant, and visit/time. If appropriate, summary statistics of the occurrence of abnormalities may be provided by treatment.

Graph of mean arterial pressure (MAP) over time will be provided by treatment. Of note MAP is defined as diastolic blood pressure + 1/3*pulse pressure, where pulse pressure =systolic blood pressure – diastolic blood pressure).

### Clinical laboratory evaluations

Summary statistics for all laboratory data will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification may be used, as appropriate, to compare baseline to the worst value. Where normal ranges are available, abnormalities in laboratory data will be listed by treatment group, participant, and visit/time.

Graphical displays of selected safety parameters (e.g. hematological parameters, thyroid and reproductive hormone levels) over time will be provided by treatment group.

For laboratory parameters which are lower or greater than the limit of quantification, the number and percentage of values below the lower limit of quantification (LLOQ) and above the upper limit of quantification (ULOQ) will be presented for categorical variables. For numerical presentation, the values less than LLOQ will be imputed as a value of 0.5×LLOQ and the values greater than ULOQ will be imputed as a value of 1.5×ULOQ.

The frequency and percentage of participants with clinically significant abnormal laboratory values shown in Table 2-2 will also be provided.

**Table 2-2 Clinically notable laboratory values**

| Parameter | Conventional Alert Value | Conventional Units | SI Alert Value | SI Units |
|---|---|---|---|---|
| **Hematology** | | | | |
| Red Blood Cell Count | >50% increase, >30% decrease | $\times 10^6/\mu L$ | >50% increase, >30% decrease | $\times 10^{12}/L$ |
| Hemoglobin | >50% increase, 30% decrease, or any value <7 | g/dL | >50% increase, >30% decrease, or any value <70 | g/L |
| Hematocrit | >50% increase, >30% decrease | % | >50% increase, >30% decrease | L/L |
| White Blood Cell Count | >50% increase, >50% decrease | $\times 10^3/\mu L$ | >50% increase, >50% decrease | $\times 10^9/L$ |
| Platelet Count | >75% increase, >50% decrease | $\times 10^3/\mu L$ | >75% increase, >50% decrease | $\times 10^9/L$ |
| **Chemistry** | | | | |
| BUN | >50% increase | mg/dL | >50% increase | mmol/L |
| Creatinine | >50% increase | mg/dL | >50% increase | µmol/L |
| Albumin | <2 | g/dL | <20 | g/L |
| Glucose | >50% increase, >50% decrease, or any value <60 | mg/dL | >50% increase, >50% decrease, or any value <3.3 | mmol/L |
| Total Bilirubin | >100% increase | mg/dL | >100% increase | µmol/L |
| Creatine phosphokinase (CPK) | >300% increase | U/L | >300% increase | U/L |
| AST (SGOT) | >150% increase | U/L | >150% increase | U/L |
| ALT (SGPT) | >150% increase | U/L | >150% increase | U/L |
| Alkaline phosphatase | >100% increase | U/L | >100% increase | U/L |
| Sodium | >5% increase, or any value >150 | mEq/L | >5% increase, or any value >150 | mmol/L |
| Potassium | >20% increase, >20% decrease, or any value >5.3 | mEq/L | >20% increase, >20% decrease, or any value >5.3 | mmol/L |

| Parameter | Conventional Alert Value | Conventional Units | SI Alert Value | SI Units |
|---|---|---|---|---|
| Chloride | >10% increase, >10% decrease | mEq/L | >10% increase, >10% decrease | mmol/L |
| Calcium | >10% increase, >10% decrease | mg/dL | >10% increase, >10% decrease | mmol/L |
| Uric Acid | >50% increase | mg/dL | >50% increase | mmol/L |

### Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time. The listing will contain ADA status (negative or positive) and for ADA-positive samples a titer and ADA neutralization potential of TIN816 and/or endogenous CD39. Subjects with one or more treatment emergent (induced or boosted) ADAs are counted as ADA-positive subjects and they will be summarized by treatment arm to derive an ADA incidence. Incidences for neutralizing ADAs will be assessed as well, if appropriate. Visualizations overlaying ADA status including characterizations, along with PK concentration and potentially efficacy read-outs, will be presented.

### Deaths

The number of deaths resulting from treatment-emergent AEs will be summarized by SOC and PT. Death refers to treatment-emergent adverse events with fatal outcome. In addition, a separate summary of death events including on treatment and post treatment deaths will be provided if appropriate.

All the deaths in the clinical database will be listed.

### 2.6.2 Sensitivity analyses

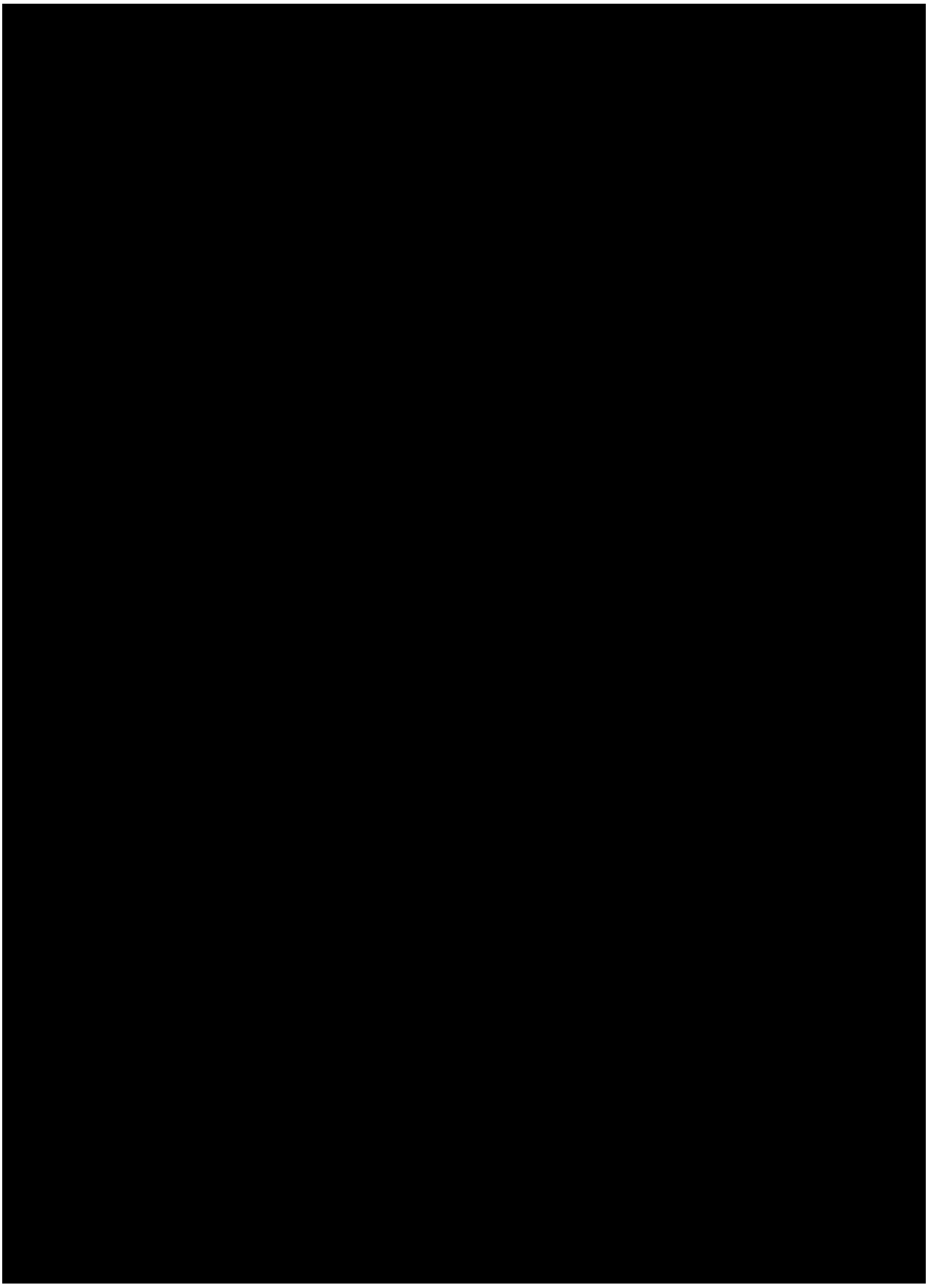
Not applicable.

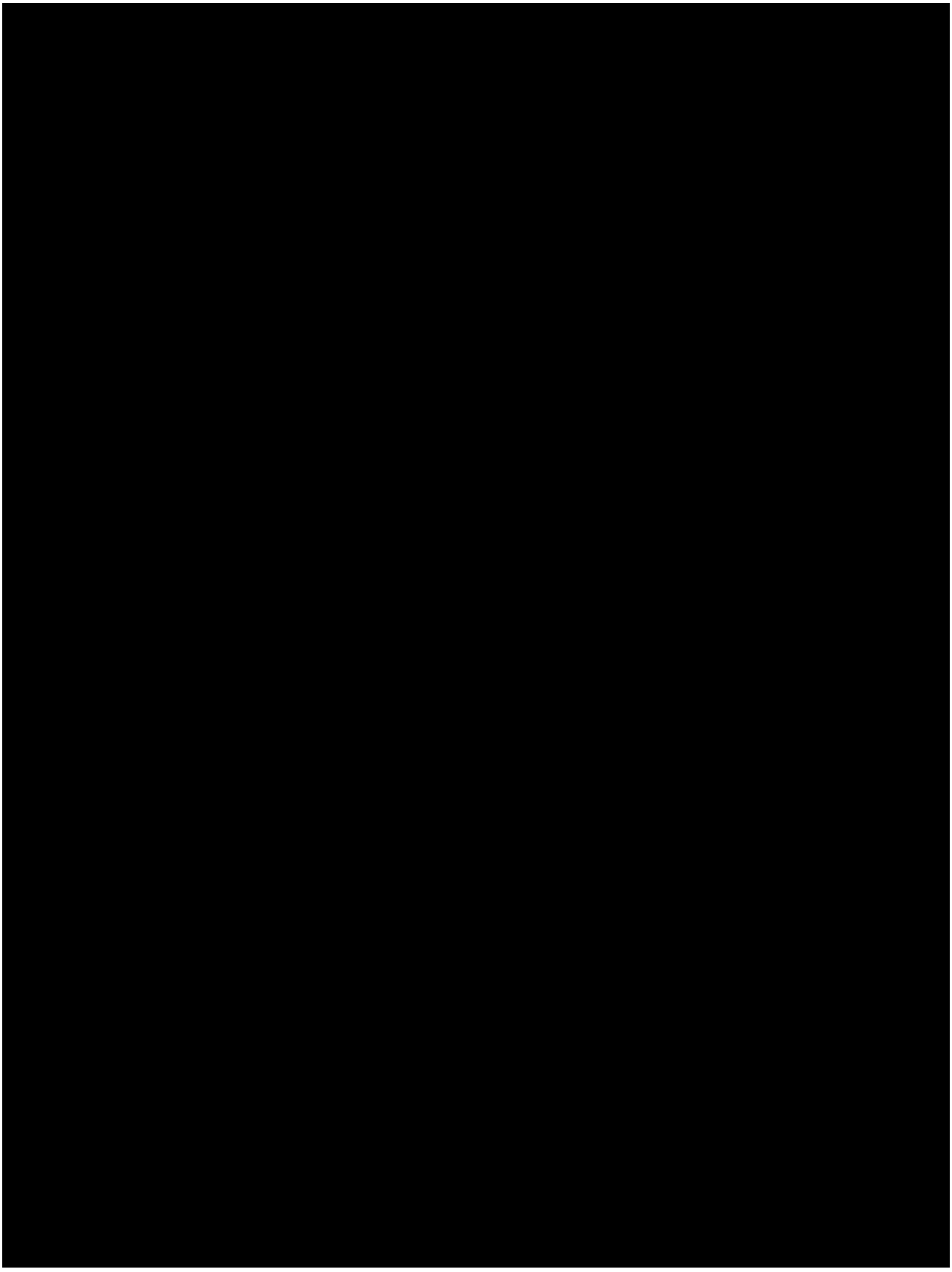
### 2.6.3 Supportive analyses

Not applicable.

## 2.7 Safety analyses

Please refer to Section 2.6.





[redacted]

## 2.11 Interim analysis

An interim analysis is planned when approximately 8 patients complete Day 14 visit. The study will continue to recruit participants while this interim analysis is being completed up to a cap of 12 participants. The study will continue without modification if a similar PK profile of TIN816 to that in the healthy volunteers (CTIN816A02101) is confirmed. Otherwise, the study may be amended with options of additional arms for testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion. The total sample size may increase to provide adequate PK data after dose level and/or dose regimens are changed. In the circumstance that the data from the first IA does not provide sufficient PK data to support the phase 2b, an additional IA will be added when all 20 patients complete Day 14 visit.

# 3 Sample size calculation

## 3.1 Primary endpoint

The sample size was determined to achieve a target margin of error of the mean for PK parameters $C_{max}$ and $AUC_{inf}$. The assumption of geometric coefficient of variation (GCV) rate was referenced from FIH study (CTIN816A02101) interim safety report.

The proposed sample size of 15 participants in TIN816 study treatment arm is sufficient to achieve a target margin of error not larger than 15% of the geometric mean (half-width of a 2-sided 95% confidence interval for the PK parameters) assuming geometric coefficient of variant (GCV) is 0.25 in $AUC_{inf}$ or $C_{max}$. It will also be able to exclude a 1.5-fold change in AUCinf or $C_{max}$ assuming GCV increased variability of 0.75.

Different GCV rates and corresponding precision of confidence interval are shown in below table.

**Table 3-1 Sensitivity of confidence interval precision to change in assumption for GCV rate**

| GCV rate * | Width of 95% confidence interval |
|---|---|
| 0.25 | [geometric mean/1.15, geometric mean x 1.15] |
| 0.50 | [geometric mean/1.31, geometric mean x 1.31] |
| 0.75 | [geometric mean/1.47, geometric mean x 1.47] |
| *Geometric mean of $AUC_{inf}$ and $C_{max}$ for 2 mg/kg are 8% and 22%, respectively in FIH study (CTIN816A02101) interim safety reports | |

## 3.2 Secondary endpoints

Not applicable.

# 4 Change to protocol specified analyses

[redacted]

Pharmacokinetic parameters from non-compartmental analysis in Table 2-1 are normalized by actual dose.

Treatment emergent adverse event will not be summarized by treatment, SMQ and preferred term.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 AE date imputation

#### AE end date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study has been defined as in Section 2.1.1.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (date of last contact, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (date of last contact, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

#### AE start date imputation

Rules for imputing the AE start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

| | Day | Month | Year |
|---|---|---|---|
| **Partial Adverse Event Start Date** | Not used | MON | YYYY |
| **Treatment Start Date** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| **YYYY MISSING** | **( 1 )** No convention | **( 1 )** No convention | **( 1 )** No convention | **( 1 )** No convention |
| **YYYY < TRTY** | **( 2.a )** Before Treatment Start | **( 2.b )** Before Treatment Start | **( 2.b )** Before Treatment Start | **( 2.b )** Before Treatment Start |
| **YYYY = TRTY** | **( 4.a )** Uncertain | **( 4.b )** Before Treatment Start | **( 4.c )** Uncertain | **( 4.c )** After Treatment Start |

| YYYY > TRTY | ( 3.a ) After Treatment Start | ( 3.b ) After Treatment Start | ( 3.b ) After Treatment Start | ( 3.b ) After Treatment Start |
|---|---|---|---|---|

Before imputing AE start date, find the AE start reference date.

1. If the imputed AE end date is complete and the imputed AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete imputed AE end date is available and the imputed AE start date is greater than the imputed AE end date, then imputed AE start date should be set to the imputed AE end date.

### 5.1.2 Concomitant medication date imputation

#### Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study has been defined as in Section 2.1.1. Concomitant medication end dates will not be imputed for ongoing records.

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of date of last contact and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of date of last contact and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the date of last contact + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

### Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

| | Day | Month | Year |
|---|---|---|---|
| **Partial CMD Start Date** | Not used | MON | YYYY |
| **Treatment Start Date** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| **YYYY MISSING** | **( 1 )** Uncertain | **( 1 )** Uncertain | **( 1 )** Uncertain | **( 1 )** Uncertain |
| **YYYY < TRTY** | **( 2.a )** Before Treatment Start | **( 2.b )** Before Treatment Start | **( 2.b )** Before Treatment Start | **( 2.b )** Before Treatment Start |
| **YYYY = TRTY** | **( 4.a )** Uncertain | **( 4.b )** Before Treatment Start | **( 4.a )** Uncertain | **( 4.c )** After Treatment Start |
| **YYYY > TRTY** | **( 3.a )** After Treatment Start | **( 3.b )** After Treatment Start | **( 3.b )** After Treatment Start | **( 3.b )** After Treatment Start |

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
   c. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

d. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:
   e. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   f. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   g. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete imputed CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

## 5.2 Statistical models

### 5.2.1 Rule of exclusion criteria of analysis sets

Considering the relatively low sample size in the study there are no protocol deviations which will lead to exclusion of patients from any analysis set.

# 6 Reference

Delgado C, Baweja M, Crews DC, et al (2021) A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis; 32:2994–3015.